

REMARKS

Claims 1-10 have been cancelled and new claims 11-18 have been added. Claims 11-18 are currently pending in the application. All pending claims are set forth in Exhibit A with amendments shown (if applicable).

Attorney for Applicants gratefully acknowledges the interview with the Examiner on 12 July 2002 in which the proposed new claims and rejections were discussed. The new claims have been submitted to more clearly describe Applicants' invention and to overcome rejections based on 35 U.S.C. 112 second paragraph.

Basis new claims are as follows:

New Claim(s)	Term/Phrase	Basis
11	"1 to 500 atoms" in reference to M.	Page 17, line 23.
11	"group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron" in reference to M.	Page 17, lines 25-26. Fig. 6.
11	"12 to 60 nucleotides" in reference to T.	Page 41, lines 27-29.
11	"a distinct charge/mass ratio"	Page 23, line 35.
12	"D-M-N-T"	Claim 2.
12	"1 to 300 atoms" in reference to M.	Page 17, line 23.
13	"D is a fluorescent label or an electrochemical label"	Page 43, lines 21-27.
14	"from 5 to 100" in reference to plurality.	Page 30, lines 2-3.
15	"cleavase"	Page 42, lines 13-43.
16	"fluorescein"	Fig. 6
17	"capture ligand is biotin"	Claim 6.
18	"capture agent attached to solid support"	Claim 1.

No new matter has been added by the amendments. Reconsideration is respectfully requested.

Provisional Double Patenting

The Examiner provisionally rejected claims 1-3, 5-7, and 10 under the doctrine of obviousness-type double patenting with respect to the following claims of the following copending applications:

Claims	Ser. No. of Copending Application
1-9	09/825,245
1-7	09/825,246
1-4	09/824,861
1-4	09/824,851

Applicants have enclosed appropriate Terminal Disclaimers with respect to the above pending applications to overcome the above rejections. Accordingly, Applicants respectfully request that the above rejections be withdrawn.

Objections to Claims

The Examiner objected to claims 1-9 because of typographical errors in the symbol "U₁" and to claim 4 because of inappropriate dependency.

Applicants respectfully submit that the new claims have obviated these objections by removing the symbol and correcting claim dependency. Accordingly, Applicants respectfully request that the objections be withdrawn.

Rejections Under 35 U.S.C. 112

The Examiner rejected claims 1-15 under 35 U.S.C. 112 second paragraph because of various phrases and terms thought to be vague or confusing.

Applicants respectfully disagree with these rejections, particularly in view of the above amendments. Each instance of vague or confusing language was discussed by Attorney for Applicants and the Examiner in the interview of 12 July 2002 and it was agreed that the language of the pending claims overcomes the rejections based on 112 second paragraph. Accordingly, Applicants request that the rejections be withdrawn.

Rejection Under 35 U.S.C. 102

The Examiner rejected claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Grossman (5,470,705). The Examiner argues as follows: Grossman discloses oligonucleotide binding compounds having polymeric tails that can be electrophoretically separated to permit multiplexed measurements. Grossman does not explicitly show a "capture ligand" on his probe compounds; however, probe capture is shown inherently by the hybridization of probes to a target polynucleotide, for example, as shown in Fig. 20B.

Applicants respectfully disagree. First, Applicants' capture ligand is not an inherent part of an oligonucleotide probe that operates by specific hybridization, as suggested by the Examiner's argument. It is a distinct moiety attached to one of the nucleotides of the probe for the specific purpose of removing from electrophoretic analysis those probes that are not cleaved (i.e. those probes that do not release an electrophoretic tag, or "c-tag reporter"). Figure 26 and 27 of the application show the result of using such a capture ligand: The same analysis was carried out in

two experiments. In one experiment, uncleaved probe was not removed by capture ligands (results shown in Fig. 26), and in the other experiment, uncleaved probe was removed by capture ligands (results shown in Fig. 27). A remarkable improvement in signal can be seen that results from the use of the capture ligand to remove uncleaved probe. Not only does Grossman not disclose the distinct element of a "capture ligand," but neither does Grossman teach the function, or even the desirability of the function, of Applicants' capture ligand.

Second, the "inherent" capture in Grossman is by a different mechanism (specific hybridization) and for a different purpose than Applicants' use of a capture ligand. In Grossman, there are two "capture" events shown in Fig. 20B. The first is capture of the probe by its hybridization to a target polynucleotide. The second is capture of the target polynucleotide by its hybridization to an oligonucleotide attached to a solid phase support. The purpose of the first "capture" is to detect the presence or absence of a target sequence, and the purpose of the second is (i) to reduce the complexity of a hybridization reaction by isolating a subset of target polynucleotides, and/or (ii) to permit non-hybridizing probe to be washed away. Neither purpose relates to Applicants' use of a capture ligand, which is to remove uncleaved probe prior to electrophoretic analysis.

Accordingly, Applicants submit that the equivalent of the capture ligand in Applicants' invention is not disclosed identically in Grossman, and respectfully request that the rejection under 35 U.S.C. 102(b) be withdrawn.

Rejections Under 35 U.S.C. 103

The Examiner rejected claim 5-8 and 10 under 35 U.S.C. 103(a) as being unpatentable over Grossman (5,470,705) in view of Babon (5,851,770). The Examiner applies Grossman as described above. Babon discloses use of a capture ligand, such as biotin, to capture on a solid phase support various hetero- and homoduplexes that may or may not contain mismatched basepairs. Captured duplexes are treated with a mismatch-recognizing nuclease that cleaves the captured sequences at mismatch locations to release fragments which are then analyzed by electrophoresis. The Examiner argues that it would be obvious to one of ordinary skill to modify the probes of Grossman to include the capture ligands of Babon, thereby obtaining Applicants' invention. One of ordinary skill would be motivated to make such a combination because of the advantages of being able to wash away unbound probe in the solid phase system disclosed by Babon.

Applicants respectfully disagree. First, the capture ligand disclosed by Babon (like Grossman) is attached to a target sequence, not a probe, and it is the target sequence that is cleaved in Babon, not a probe. This is in contrast to Applicants' invention where the capture ligand is attached to probes, and the probes are cleaved to release eTag reporters. Second, Grossman and Babon neither disclose nor suggest the desirability of placing a capture ligand on the probe, as described by Applicants. In this regard, Applicants direct the Examiner to Figs. 26 and 27 of the application which show the dramatic improvement in signal that occurs by use of a capture ligand on the probe, as discussed above. There is no equivalent observation, or other suggestion, in either Grossman or Babon that would motivate one of ordinary skill to place the capture ligand of Babon on the probes of Grossman. Applicant submit that the combination of Grossman and Babon would not lead one of ordinary skill to Applicants' invention without an independent inventive contribution, and accordingly respectfully request that the rejection be withdrawn.

The Examiner rejected claim 9 under 35 U.S.C. 103(a) as being unpatentable over Grossman in view of Huie (5,470,967). The Examiner applies Grossman as above and cites Huie for the disclosure of "nuclease-resistant" linkages in oligonucleotides. The Examiner argues that it would have been obvious to one of ordinary skill to introduce nuclease-resistant linkages into the probes of Grossman using the teaching of Huie.

Applicants respectfully disagree. Neither Grossman nor Huie teach or suggest the analytical problem created by using a nuclease to cleave a probe. A nuclease does not always cleave every probe at precisely the same inter-nucleoside linkage, as is illustrated diagrammatically in Figure 3A-C of the application. As a result, such cleavage can give rise to spurious peaks upon electrophoretic separation. There is no suggestion or appreciation of this problem in either reference. In particular, Huie is concerned with the use of nuclease resistant oligonucleotides for therapeutic purposes; thus, the application of such compounds in analytical applications is simply not disclosed or suggested. Likewise, the thrust of Grossman is the use of ligation to modify probes for separation. The mention of nuclease modified probes is only a minor aspect of the Grossman invention¹; thus, potential applications of nuclease-resistant oligonucleotides is not

1. Several probe modification schemes are disclosed by Grossman, including ligation (Figs. 7A-D, 9, 10A-C, 18A-B; col. 12 (line 61) to col. 16 (line 53); and Examples 7 and 8), probe extension (col. 18 (line 56) to col. 19 (line 21); no example), and fragment cleavage (col. 19 (line 22) to col. 20 (line 44); no example). By the number of words and figures devoted to each, clearly ligation is the primary focus of Grossman's probe modification.

disclosed or suggested. Therefore, Applicants submit that one of ordinary skill would not be motivated to combine the respective teachings and obtain Applicants' invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and that the claims be allowed and the application quickly passed to issue.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account 50-2266.

Respectfully submitted,



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Enclosures:

825, 246

Terminal Disclaimers for USSNs: 09/825,245; 09/824,245;
09/824,851; and 09/824,861.

Petition for Time Extension

~~Patent Application Fee Determination Record~~ *Fee Transmittal form*

Facsimile Transmittal cover sheet with deposit account withdrawal
authorization.

Exhibit A
Currently Pending Claims Showing Amendments (if applicable)

-11. A kit for detecting the presence or absence of one or more of a plurality nucleotide sequences in a sample, the kit comprising a plurality of electrophoretic probes selected from the group defined by the formula:



wherein:

(D, M)-N is an e-tag reporter;

D is a detection group;

M is a mobility modifier consisting of from 1 to 500 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron;

N is a nucleotide; and

T is an oligonucleotide specific for at least one of the plurality of nucleotide sequences, each T having a length in the range of from 12 to 60 nucleotides such that at least one nucleotide of T has a capture ligand attached;

and wherein each e-tag reporter of the plurality of electrophoretic probes has a distinct charge/mass ratio so that the e-tag reporters form distinct peaks upon electrophoretic separation.

12. The kit of claim 11 wherein said formula is D-M-N-T and wherein M is a mobility modifier consisting of from 1 to 300 atoms selected from the group consisting of carbon, hydrogen, oxygen, phosphorus, nitrogen, sulfur, and boron.

13. The kit of claim 12 wherein D is a fluorophore, chromophore, or an electrochemical label.

14. The kit of claim 13 wherein said plurality is in the range of from 5 to 100.

15. The kit of claim 14 further including a cleavase.

16. The kit of claim 14 wherein said fluorescent label is a fluorescein.

17. The kit of claim 14 wherein said capture ligand is biotin.
18. The kit of claim 14 further including a capture agent attached to a solid support.—